The Amendments to the Claims

The feature of claim 2 has been incorporated into claim 1 as a result of the restriction requirement. Claim 2, therefore, has been cancelled as superfluous. Claims 28-37 also have been cancelled as a result of the restriction requirement. Claims 1 and 3-27 have been amended to address matters of form, specifically to remove reference to non-elected subject matter. Applicants reserve the right to pursue any cancelled subject matter in a continuation, continuation-in-part, divisional, or other application. Cancellation of any subject matter should not be construed as abandonment of that subject matter. No new matter has been added by way of these amendments. Separate documents setting forth the precise changes to the claims, as well as the text of all of the pending claims, are enclosed herewith.

The Pending Claims

Claims 1 and 3-27 are pending and are directed to an adenoviral vector comprising a nucleic acid sequence encoding pigment epithelium-derived factor (PEDF) or a therapeutic fragment thereof operably linked to regulatory sequences necessary for expression of the PEDF or a therapeutic fragment thereof.

The Office Action

The Office Action has set forth the following rejections:

(i) Claims 1-2, 21, and 24-27 are rejected under 35 U.S.C. § 103(a) for allegedly being unpatentable over U.S. Patent 6,288,024 ("the Bouck '024 patent") in view of U.S. Patent 5,827,702 ("the Cuthbertson '702 patent").

(ii) Claims 1-15, 21, and 24-27 are rejected under 35 U.S.C. § 103(a) for allegedly being unpatentable over the Bouck '024 patent in view of the Cuthbertson '702 patent, U.S. Patent 6,113,913 ("the Brough '913 patent"), and U.S. Patent 6,225,113 ("the Brough '113 patent").

(iii) Claims 1-2, 18-21, and 24-27 are rejected under 35 U.S.C. § 103(a) for allegedly being unpatentable over the Bouck '024 patent in view of the Cuthbertson '702 patent and U.S. Patent 5,962,311 ("the Wickham '311 patent").

Reconsideration of these rejections is hereby requested.

Discussion of Rejections

To establish a *prima facie* case of obviousness the burden is on the Patent Office to establish three criteria: (i) the prior art references must teach or suggest all of the claim limitations, (ii) there must be some suggestion or motivation to combine reference teachings, and (iii) there must be a reasonable expectation of success. M.P.E.P. § 2143; *In re Vaeck*, 20 USPQ2d 1438 (Fed. Cir. 1991).

All of the pending claims (i.e., claims 1 and 3-27) are directed to an adenoviral vector comprising a nucleic acid sequence encoding PEDF or a therapeutic fragment thereof. The nucleic acid sequence is operably linked to regulatory sequences necessary for expression of PEDF or the therapeutic fragment.

The Bouck '024 patent teaches a method of inhibiting angiogenesis within a tissue by providing exogenous SLED protein (described as a PEDF or fragment) to cells associated with the tissue. The Bouck '024 patent does not describe an adenoviral vector comprising a nucleic acid sequence encoding PEDF or a therapeutic fragment thereof. The Bouck '024 patent merely describes administering SLED polypeptides to a tissue or cell, for example, by administering full-length SLED polypeptides directly to a cell culture (Examples 1-4 and 6), by implanting pellets containing the SLED protein directly into rat corneas (Example 5), or by precipitating bacterial plasmids containing a SLED expression cassette onto gold particles and administering the plasmids directly to the skin of mice using a gene gun (Example 7).

Although the Bouck '024 patent mentions the use of an adenoviral vector in the context of "any suitable vector" (column 6) suitable for use in the method of inhibiting angiogenesis, the Bouck '024 patent does not demonstrate the use of such an adenoviral vector, nor, in fact, does the Bouck '024 patent demonstrate the use of any other viral vector in the method. Furthermore, the Bouck '024 patent gives no guidance as to desirable characteristics necessary for the development of a suitable viral vector for administering SLED polypeptides. Administering SLED polypeptides directly to a cell culture, implanting SLED polypeptides into rat corneas, or administering plasmids expressing SLED directly to the skin of mice, does not demonstrate a reasonable expectation of success for a viral vector, for example, an adenoviral vector, comprising a nucleic acid sequence encoding PEDF or a therapeutic fragment thereof. Thus, not only does the Bouck '024 patent not describe the inventive adenoviral vectors at all, one of ordinary skill in the art would not have a reasonable expectation of success in constructing such an adenoviral vector comprising a nucleic acid encoding PEDF or a therapeutic fragment thereof.

The Cuthbertson '702 patent teaches a method for generating a genetically engineered *in situ* ocular cell by contacting an ocular cell with exogenous nucleic acid such that the nucleic acid is taken up by the cell and expressed therein. The Cuthbertson '702 patent does not describe an adenoviral vector comprising a nucleic acid sequence encoding PEDF or a therapeutic fragment thereof. In fact, the Cuthbertson '702 patent does not so much as mention the use of a PEDF polypeptide or a therapeutic fragment thereof, but merely discloses the delivery of the β-galactosidase gene to rat corneal epithelium or choroid ocular cells using an E1-deficient adenoviral vector expressing the β-galactosidase gene (Examples 1-3). Thus, the Cuthbertson '702 patent does not teach or suggest the claimed adenoviral vectors.

Moreover, with respect to those pending claims that recite that the inventive adenoviral vectors further comprise a nucleic acid sequence encoding another therapeutic substance such as an anti-angiogenic substance (i.e., claims 21-27), the Office Action asserts that the Bouck '024 patent discloses the use of SLED in combination with other anti-angiogenic agents (Office Action, page 5). However, the Bouck '024 patent does not describe an adenoviral vector comprising a nucleic acid sequence encoding PEDF (or a therapeutic fragment thereof) linked to regulatory sequences necessary for expression of the nucleic acid sequence and further comprising an anti-angiogenic substance. The Bouck '024 patent does not even describe a viral vector, such as an adenoviral vector, comprising an anti-angiogenic substance, let alone a viral vector, such as an adenoviral vector, comprising *both* an anti-angiogenic substance *and* a nucleic acid sequence encoding a PEDF or a therapeutic fragment thereof. The Cuthbertson '702 patent does not even describe the administration of an anti-angiogenic substance at all, let alone the co-administration of such a substance with a PEDF or a therapeutic fragment thereof, particularly wherein the anti-angiogenic substance is a soluble VEGF-R1 receptor (as recited in claim 26) or is linked to an endoplasmic reticulum localization signal peptide (as recited in claim 27). As such, neither the Bouck '024 patent nor the Cuthbertson '702 patent teach or suggest an adenoviral vector comprising a nucleic acid encoding PEDF (or a therapeutic fragment thereof) and further comprising an anti-angiogenic substance.

The Office Action does not point to anything in the Bouck '024 patent or the Cuthbertson '702 patent that would lead one of ordinary skill in the art to combine their representative disclosures, let alone in the manner necessary to arrive at the present invention. Indeed, even if the disclosures of the Bouck '024 patent and the Cuthbertson '702 patent are combined, the inventive adenoviral vector does not necessarily result.

Therefore, the Bouck '024 patent in view of the Cuthbertson '702 patent does not render the inventive adenoviral vector obvious.

The Office Action, appreciating the deficiencies of the Bouck '024 patent and the Cuthbertson '702 patent, relies on the Brough '913 patent and the Brough '113 patent to cure the substantial defects in the combination of the Bouck '024 patent with the Cuthbertson '702 patent.

Applicants assert that, not only is the combination of the Bouck '024 patent and the Cuthbertson '702 patent not sufficient to demonstrate a *prima facie* case of obviousness for the reasons set forth above, the Brough '913 and Brough '113 patents do not cure the defects presented by such a combination. The Brough '913 patent describes replication-deficient adenoviral vectors. The Brough '113 patent describes adenoviral vectors deficient in the E4 gene and comprising HSV ICP0, and such adenoviral vectors further comprising a MAR or LCR sequence. Neither the Brough '913 patent nor the Brough '113 patent teach or suggest an adenoviral vector comprising a nucleic acid encoding PEDF or a therapeutic fragment thereof. In fact, neither patent even so much as mentions PEDF or a therapeutic fragment thereof. Furthermore, the Office Action does not point to anything in the Bouck '024 patent, the Cuthbertson '702 patent, or either of the Brough patents that would lead one of ordinary skill in the art to combine their representative disclosures, let alone in the manner necessary to arrive at the adenoviral vector of the present invention with a reasonable expectation that such adenoviral vector would be suitable for its intended purpose. Thus, the Bouck '024 patent in view of the Cuthbertson '702 patent, the Brough '913 patent, and the Brough '113 patent does not render the inventive adenoviral vectors obvious.

The Office Action also relies on the Wickham '311 patent as a cure for the defective Bouck '024 patent and Cuthbertson '702 patent combination.

Applicants submit that the combination of the Bouck '024 patent and the Cuthbertson '702 patent is not sufficient to demonstrate a *prima facie* case of obviousness for the reasons set forth above, and the deficiencies in the combination are not cured by the addition of the Wickham '311 patent. The Wickham '311 patent describes adenoviral vectors comprising short-shafted adenoviral fiber genes. The Wickham '311 patent does not teach or suggest an adenoviral vector comprising a nucleic acid encoding PEDF or a therapeutic fragment thereof, nor does the Wickham '311 patent teach or suggest such an adenoviral vector further comprising a chimeric fiber protein. The Wickham '311 patent does not so much as even mention PEDF or a therapeutic fragment thereof. The Office Action does not point to anything in the Bouck '024 patent, the Cuthbertson '702 patent,

or the Wickham '311 patent that would motivate one of ordinary skill in the art to combine their representative disclosures in the manner necessary to arrive at the adenoviral vector of the present invention with a reasonable expectation that such adenoviral vector would be suitable for its intended purpose. Thus, the Bouck '024 patent in view of the Cuthbertson '702 patent, and the Wickham '311 patent does not render the inventive adenoviral vector obvious.

Under the circumstances, the present invention must be considered to be unobvious over the cited references. The rejections should be withdrawn.

Conclusion

The application is considered in good and proper form for allowance, and the Examiner is respectfully requested to pass this application to issue. If, in the opinion of the Examiner, a telephone conference would expedite the prosecution of the subject application, the Examiner is invited to call the undersigned agent.

Respectfully submitted,

Heather Kissling, Reg. No. 45.790
LEYDIG, VOIT & MAYER, LTD.
Two Prudential Plaza, Suite 4900
180 North Stetson
Chicago, Illinois 60601-6780
(312) 616-5600 (telephone)
(312) 616-5700 (facsimile)

Date: July 9, 2002

In re Appln. of Kovesdi et al.
Application No. 09/599,997

CERTIFICATE OF MAILING

I hereby certify that this RESPONSE TO OFFICE ACTION (along with any documents referred to as being attached or enclosed) is being deposited with the United States Postal Service on the date shown below with sufficient postage as first class mail in an envelope addressed to: Commissioner for Patents, Washington, D.C. 20231.

Date: July 9, 2003 Kilma Del Mayo